

ToxCast: Developing Predictive Signatures of Chemically Induced Toxicity

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Abstract : ToxCast, the United States Environmental Protection Agency's chemical prioritization research program, is developing methods for utilizing computational chemistry, bioactivity profiling and toxicogenomic data to predict potential for toxicity and prioritize limited testing resources. In the proof-of-concept phase, ToxCast is evaluating chemicals with an existing, rich toxicological database in order to provide an interpretive context for the high throughput screening (HTS) data. This set of 320 reference chemicals is largely derived from active ingredients in food-use pesticides and represents numerous structural classes and phenotypic outcomes, including tumorigens, developmental and reproductive toxicants, neurotoxicants and immunotoxins. The goal of the ToxCast program is to develop signatures predictive of *in vivo* toxicity, based on the combined use of physicochemical properties, the traditional independent variables in structure activity models, as well as *in vitro* bioactivity data derived from a broad spectrum of over 400 biochemical, cell-based, or gene expression assays. In later phases of ToxCast, the HTS signatures derived for chemicals with toxicity data gaps will be compared with those of well-characterized chemicals, and significant signature matches will identify priority candidates for further testing in traditional animal bioassays. ToxCast data are being generated through a series of external contracts, and by collaborations within EPA and with the National Institutes of Health Chemical Genomics Center. Development of the supporting chemo-informatic infrastructure and initial results from the proof-of-concept phase indicate that this approach will succeed. [This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.]

Transforming Toxicology



Phased Development of ToxCast

Phase	Number of Chemicals	Chemical Criteria	Purpose	Number of Assays	Cost per Chemical	Target Date
I	320	Data Rich (prioritized)	Signature Development	>400	\$2k	FY07-08
IIa	>100	Data Rich Chemicals	Validation	>400	\$15-20k	FY09
IIb	>100	Known Mechanism Toxicants	Extrapolation	>400	\$15-20k	FY09
IIIc	>300	Expanded Structure-Use Categories	Extension	>400	\$15-20k	FY10
III	Thousands	Data poor	Prediction and Prioritization	???	\$10-15k	FY11-12

- >Affordable science-based system for categorizing chemicals
- >Increasing confidence as database grows
- >Identifies potential mechanisms of action
- >Refines and reduces animal use for hazard ID and risk assessment

www.epa.gov/ncct/toxcast

